REVIEW ARTICLE

Prevention of Esophageal Variceal Rebleeding

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The rate of rebleeding of esophageal varices remains high after cessation of acute esophageal variceal hemorrhage. Many measures have been developed to prevent the occurrence of rebleeding. When considering their effectiveness in reduction of rebleeding, the associated complications cannot be neglected. Due to unavoidable high incidence of complications, shunt surgery and endoscopic injection sclerotherapy are now rarely used. Transjugular intrahepatic portosystemic stent shunt was developed to replace shunt operation but is now reserved for rescue therapy. Nonselective beta-blockers alone or in combination with isosorbide mononitrate and endoscopic variceal ligation are currently the first choices in the prevention of variceal rebleeding. The combination of nonselective beta-blockers and endoscopic variceal ligation appear to enhance the efficacy. With the advent of newly developed measures, esophageal variceal rebleeding could be greatly reduced and the survival of cirrhotics with bleeding esophageal varices could thereby be prolonged. [*J Chin Med Assoc* 2006;69(12):553–560]

Key Words: banding ligation, beta-blocker, sclerotherapy, transjugular intrahepatic portosystemic stent shunt, variceal rebleeding

Introduction

Esophageal variceal hemorrhage is a devastating complication of portal hypertension. It is associated with a high morbidity and mortality.[1] The mechanisms underlying rupture of esophageal varices are poorly defined. It has been demonstrated that the portal pressure is usually >10 mmHg in patients who develop esophageal varices and the portal pressure generally exceeds 12 mmHg in patients with rupture of varices. To control acute variceal bleeding, treatment modalities such as vasoconstrictors, balloon tamponade, endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) may be employed.[2,3] Once acute bleeding is successfully controlled, rebleeding may occur in approximately 2-thirds of patients if further preventive measures are not taken.[1] Several factors have been noted to be associated with the occurrence of variceal rebleeding; portal pressure, poor liver reserve, sizes of varices, red color signs on varices, treatment modalities of acute bleeding, infection and portal vein thrombosis have all been presumed to be related to variceal rebleeding.[4–6] Except for moribund patients, measures should be taken to reduce variceal rebleeding episodes to improve patient survival. The time frame of variceal rebleeding can be divided into very early rebleeding (within 5 days of acute bleeding), early rebleeding (within 6 weeks of acute bleeding) and delayed rebleeding. By definition, prevention of variceal rebleeding starts on day 6.[7] Numerous modalities have been developed to prevent variceal rebleeding. The measures used to prevent very early rebleeding and delayed rebleeding are quite different. This review will focus on the methods used for secondary prophylaxis excluding very early rebleeding. Which method is the most popular? Which method has the least possibility of inducing complications? What kind of complications may be encountered in patients who receive preventive therapy? If initial preventive therapy has failed in a patient, what should be the second line measure? These questions are addressed in this comprehensive review.

Surgery

Approximately 3 decades ago, shunting operation and devascularization procedures were widely adopted to prevent variceal rebleeding. Undeniably, operative

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measures can generally achieve a rather low incidence of rebleeding. Shunting operations such as Warren shunt or Sarfeh's procedures or the devascularization method developed by Sugiura and Futagawa all achieved a rebleeding rate of < 10%.[8,9] However, these procedures are time-consuming and technically difficult operations, requiring great surgical expertise.[8,9] It was presumed that a selective shunt might have a lower incidence of hepatic encephalopathy than a nonselective shunt. A large study from the United States comparing distal splenorenal shunt (DSS) and portosystemic shunt (PSS) suggested that 30-day operative mortality was 9% for DSS patients and 13% for PSS patients, and rebleeding rate was 18% for the DSS group and 12% for the PSS group (not significantly different), with encephalopathy occurring in 51% of the DSS group and in 45% of the PSS group (not significantly different).[10] Child-Pugh class A patients are good candidates for surgical intervention. Though patients with poor hepatic reserve treated with shunt operation can still achieve a rather low variceal rebleeding rate, they may experience high intraoperative mortality or serious complications. With the advent of EIS around 1980, surgical modality gradually yielded to EIS because of the advantages of the lower risk of complications as well as possibly improved survival. The other disadvantage of shunting operation is that it may increase technical difficulty when patients receive liver transplantation. Nowadays, surgery is reserved for patients with repeated bouts of rebleeding despite repeated endoscopic treatments. After the development of transjugular intrahepatic portosystemic stent shunt (TIPS), the role of surgery in rescue for endoscopic and/or medical treatment failure cases appears to have been replaced by TIPS.

EIS

EIS using quinine as a sclerosant was first introduced by Crafoord and Frenckner, two Swedish surgeons, in 1939.[11] Subsequently, other sclerosants such as sodium morrhuate, podidocanol, ethanolamine, and sodium tetradecyl sulfate were more widely used. The mechanisms of EIS are via injection of sclerosants resulting in tissue necrosis and finally fibrosis, causing obliteration of varices. The techniques of EIS vary widely among different clinicians. The optimal dose of sclerosants is unknown. The treatment can be injected either intravariceally or paravariceally. The treatment interval varied between a few days to weeks. Fortunately, EIS appeared to be uniformly beneficial, regardless of the variation in techniques.[12] In the full-blown era of surgery, EIS was not regarded as a useful tool to prevent variceal rebleeding and lapsed into obscurity. In 1973, Johnston and Rodgers reported that EIS could achieve a rather satisfactory effect to prevent variceal rebleeding and offer low mortality.[13] These results ignited the enthusiasm for EIS, akin to a renaissance of EIS. Since then, EIS has been widely employed to prevent variceal rebleeding, until the advent of EVL.

Four widely-cited controlled studies, the South African trial, the Los Angeles trial, the Copenhagen trial and the King's College trial, were published around 1983–1985.[14] Reduced variceal rebleeding with EIS was shown in 2 studies and improved survival was shown in only 1 study. Recurrent variceal bleeding was reduced from 54–82% in the control group to 48–55% after repeated sessions of EIS. However, a number of local and systemic complications may be encountered after EIS.[15] These complications encompass ulcer bleeding, esophageal stricture, fever, pleural effusion, bacteremia, spontaneous bacterial peritonitis, distant embolism and distant abscess. It is impossible to predict what kind of complications may be encountered in patients receiving EIS. Mortality resulting directly from complications may be noted in 2% of patients. Meta-analyses of the trials published between 1982 and 1991, comparing EIS with "nonactive" treatment, showed that patients treated with long-term EIS had a significantly lower rebleeding rate (pooled odds ratio, OR, 0.57; 95% confidence interval, CI, 0.45–0.71) and better survival than those who received only nonactive treatment (pooled OR, 0.72; 95% CI, 0.57–0.90).[16,17] During the same period, EIS was also popular in Taiwan, but no controlled trial was performed.[18,19] Among patients receiving endoscopic therapy, the variceal rebleeding rate could only be greatly reduced after variceal obliteration. In Lai et al's study, a mean of 10 sessions of EIS was required to achieve variceal obliteration.[18] This constitutes another drawback of EIS.

Medical Therapy

In 1981, Lebrec et al found that propranolol could reduce portal pressure and be used to prevent upper gastrointestinal hemorrhage related to portal hypertension.[20] The mechanisms of β-blocker action are believed to be via a reduced cardiac output and a predominant effect on the unopposed α-adrenergic receptor over the splanchnic vessels, resulting in reduced blood flow. Due to the introduction of propranolol in the prevention of variceal rebleeding, a new era began for the treatment of variceal rebleeding. Drug therapy for portal hypertension has the advantages of being simpler, lower risk and more economic than endoscopic therapies.

Nonselective β-blockers such as propranolol and nadolol are the most widely used drugs in the prevention of variceal rebleeding. Theoretically, it is better to detect the hemodynamic response in patients taking portal hypotensive drugs. The aims are reduction of the portal pressure to < 12 mmHg or > 20% compared with baseline levels. However, the measurement of portal pressure is invasive and not feasible in every patient. Thus, the dosage of β-blockers is generally based on the dosage to reduce pulse rate by 25%. Meta-analyses of the 12 randomized trials published between 1981 and 1991 showed that patients receiving β-blockers had a lower incidence of rebleeding (pooled OR, 0.69) and mortality (pooled OR, 0.78) compared to patients who did not receive any specific measure.[21] Sheen et al from Taiwan also showed that propranolol could be used to prevent variceal rebleeding.[22] The contraindications for β-blockers include asthma, bradycardia, atrioventricular block, hypotension and poorly controlled hyperglycemia. The adverse effects are usually modest, including bradycardia, chest tightness, hypotension, dizziness or impotence.

On the other hand, it has been shown that up to 1-third of patients may be non-responders to β-blockers. The addition of isosorbide mononitrate (ISMN) has been demonstrated to enhance the effect of β-blockers in reducing portal pressure through the decrease of hepatic resistance.[23] A controlled study showed that cirrhotic patients receiving propranolol and ISMN had a lower variceal rebleeding rate compared to patients who only received propranolol.[24] Hence, the combination of β-blockers and ISMN rather than using β-blockers alone to treat portal hypertension has become routine clinical practice. However, if hemodynamic study is feasible, the addition of ISMN would be unnecessary in patients who are responders to β-blockers alone.

Comparison of EIS and Medical Therapy

Both β-blockers and EIS were important and popular modalities in the prevention of variceal rebleeding during the 1980s. Studies comparing EIS and β-blockers were widely performed. A meta-analysis of 9 trials comparing β-blockers with EIS showed a significant reduction of rebleeding in favor of EIS (pooled OR, 0.64; 95% CI, 0.48–0.85).[25] However, significantly more complications were encountered in patients who received EIS,[25] while survival was similar between both therapies. A controlled trial showed that the combination of nadolol and ISMN was superior to EIS in the reduction of variceal rebleeding.[26] Hence, in the 1990s, it was recommended that β-blockers, rather than EIS, be the first choice of treatment to prevent recurrent variceal bleeding.[25]

EVL

In 1989, Stiegmann et al first introduced the application of EVL to treat esophageal varices.[27] In contrast with the chemical action induced by EIS, EVL works through mechanical strangulation by rubber bands, just like its use in the treatment of hemorrhoids. Also, different from the many technical variations practiced in EIS, the techniques of EVL appear to be unanimously similar. Initially, a single ligator associated with an overtube was employed to ligate varices. Subsequently, the multiband ligator was invented to avoid the use of an overtube and its associated complications. No significant differences in efficacy exist between these ligators. The complications of EVL include esophageal laceration or perforation (mostly due to trauma of the overtube), transient dysphagia, retrosternal pain, ulcer bleeding and bacteremia.

It is well documented that EVL requires about 1–2 sessions fewer than EIS to obliterate esophageal varices. Between 1992 and 1996, 13 studies, including 2 from Taiwan, comparing EIS and EVL in the prevention of variceal rebleeding were published.[28–32] All these studies demonstrated that EVL was superior to EIS in terms of reducing rebleeding rates and complication rates, but only 2 trials showed better survival with EVL.[27,30] A meta-analysis showed a strong benefit for EVL in reducing variceal rebleeding (pooled OR, 0.46; 95% CI, 0.35–0.60) and similar survival between patients treated with EIS and those treated with EVL.[16] Therefore, it is recommended that EVL be the endoscopic treatment of choice for the management of bleeding esophageal varices.[33] The main disadvantage of EVL is possibly a higher frequency of recurrent varices.[31,34] Fortunately, recurrent varices can usually be treated with repeated ligation. The meta-analysis did not show that EVL predisposed patients to recurrent varices.[16]

Similar to EIS, the appropriate interval between EVL sessions has not yet been determined. Most endoscopists appear to favor an interval of 1–2 weeks,[28–32] whereas I propose that an interval of 3–4 weeks is more suitable given that unhealed ulcers induced by ligation are frequently noted within 2 weeks of ligation.[5,35] EVL at a longer interval does not result in a higher rebleeding rate, and in fact, our rebleeding rate was generally lower than those of other reports.[31] A study from Japan demonstrated that EVL performed

once every 2 months was better than EVL performed once every 2 weeks in the overall rates of variceal recurrence.[36] However, EVL performed at intervals of 2 months may be inappropriate in the prevention of variceal rebleeding. The optimal interval of EVL in the prevention of variceal rebleeding awaits further study.

Comparison of EVL and Medical Therapy

The combination of β-blockers and ISMN being superior over EIS in reducing variceal rebleeding has prompted interest in how this combination compares to EVL.[26] Up to now, there has been 4 controlled trials comparing the combination of nadolol and ISMN with EVL in the prevention of variceal rebleeding,[37–40] 3 reported as full papers and 1 as an abstract (Table 1). These trials had 3 different results; ours showed that EVL was superior, another showed that pharmacologic therapy was superior and the other 2 showed equivalent efficacy for both therapies. Therefore, it is difficult to draw a conclusion about which therapy is superior. As mentioned above, 1 of the determining factors of variceal rebleeding is severity of cirrhosis. The operators' expertise in EVL, etiology of cirrhosis, and dosage of portal hypotensive drugs may also have an impact on rebleeding rates. Meta-analysis of these 4 studies showed similar survival between pharmacologic therapy and EVL.[41] Thus, either medication with nadolol plus ISMN or EVL can be used to prevent esophageal variceal rebleeding.

Combined EIS and EVL

Combination of endoscopic therapies to manage esophageal varices has been a focus of interest for endoscopists. In the context of the different mechanisms of action of EIS and EVL, combining EIS and EVL to hasten eradication of varices is anticipated. It has been noted that paraesophageal varices could be obliterated by EIS but not by EVL.[42] The combination of EIS and EVL is potentially able to reduce the possibility of recurrence. The combination of EIS and EVL can be synchronous or metachronous. Between 1996 and 2000, 7 studies were undertaken to investigate the potential benefits of combined EIS and EVL.[43] A meta-analysis of these studies failed to demonstrate any superiority over EVL alone in terms of prevention of rebleeding or mortality. Moreover, the combination may be associated with a higher complication rate of esophageal stricture. However, EIS plus EVL (the so-called sandwich method) and EIS with low-dose sclerosants following repeated EVL has been shown to reduce variceal recurrence or even reduce the incidence of variceal rebleeding.[44–46] Currently in Taiwan, sclerosants other than alcohol are not available, thus, it has become difficult to perform EIS.

Combined EIS and Medical Therapy

The combination of endoscopic therapy and drug therapy for portal hypertension is intriguing. Several reasons support the addition of drug therapy during endoscopic therapy. First, the rebleeding rate remains rather high after endoscopic therapy, especially before variceal obliteration is achieved.[4] The rebleeding rate is about 30–50% in patients treated with EIS and 20–40% in patients treated with EVL.[16,47] Second, portal hypertensive gastropathy may develop or accentuate after endoscopic therapy.[34,48,49] An increased incidence of gastric variceal bleeding[31,50] after endoscopic therapy was also noted. Third, portal pressure was noted to be elevated in approximately 70% of patients in whom variceal obliteration was achieved by either EIS or EVL.[51,52] Fourth, variceal recurrence is very common after variceal obliteration achieved by endoscopic therapy.[16] It is anticipated that all of these undesirable or untoward effects of endoscopic therapy can be abolished or alleviated by drug therapy.[48,53] A number of studies were carried out to compare the combination of propranolol and EIS with propranolol alone or EIS

Table 1. Controlled studies of endoscopic variceal ligation (EVL) *vs.* nadolol plus isosorbide mononitrate (N + I) or *vs.* propranolol plus isosorbide mononitrate (P + I) to prevent variceal rebleeding

Study	Patients (*n*)	Therapy	Rebleeding (%)	Complication (%)	Mortality (%)
Villanueva et al[37]	72/72	EVL/N + I	44/28*	12/3*	42/32
Lo et al[38]	61/60	EVL/N + I	20/42*	17/19	25/13
Patch et al[39]	51/51	EVL/P + I	54/44	14/20	22/32
Romero et al[40]	57/52	EVL + EIS/N + I	40/37	49/46	19/20

**Significant difference. EIS = endoscopic injection sclerotherapy.*

alone.[54] Unfortunately, most of the studies did not show any additional benefit of the combination of EIS and propranolol over single therapy. The variceal rebleeding rates and complications were similar between the treatments in these studies. It is very probable that each of these studies had insufficient sample size to show the benefit of the EIS and propranolol combination. Meta-analysis of the 10 studies between 1986 and 1992 suggested that the combined treatment with EIS and propranolol was significantly better than EIS alone in preventing rebleeding (pooled OR, 0.65; 95% CI, 0.46–0.92), but there was similar survival with both modalities.[54] Interpretation with caution was warned over the results of the meta-analysis because of qualitative heterogeneity.[16]

Combined EVL and Medical Therapy

Contrary to the enthusiasm about EIS plus β-blockers, the use of EVL and β-blockers in the prevention of variceal rebleeding is rarely studied. In view of the superiority of EVL over EIS and nadolol over propranolol, we compared EVL combined with nadolol and sucralfate to EVL alone in the prevention of variceal rebleeding.[54] The superiority of nadolol over propranolol includes longer half-life and renal metabolism. The use of sucralfate was to reduce ulcer bleeding provoked by EVL. After a median follow-up of 21 months, our study showed that the combination of nadolol, sucralfate and EVL was superior to EVL alone in terms of variceal rebleeding rates (12% *vs.* 29%) and variceal recurrence (26% *vs.* 50%). We presumed that the benefits of combination therapy were primarily from nadolol rather than sucralfate, since the incidence of ulcer bleeding during the course of EVL was appreciably low. A similar study by de la Pena et al also suggested that the combination of EVL and β-blockers was superior to EVL alone in reducing variceal rebleeding as well as in the prevention of variceal recurrence (Table 2).[55] However, their patients who were treated with EVL plus nadolol had a higher frequency of complications, mostly due to the use of β-blockers.

On the other hand, it is still unknown as to whether or not EVL enhances the efficacy of β-blockers plus ISMN in the prevention of recurrent variceal bleeding. We have performed such a study and the results demonstrated that combined EVL with drug therapy had a variceal rebleeding rate of 28%, which was marginally significantly lower than the 48% achieved in patients treated with drug therapy only ($p=0.05$).[56] A similar study from Spain with short-term follow-up showed that the addition of EVL to pharmacologic therapy reduced the frequency of variceal rebleeding but resulted in a higher frequency of severe complications that required hospitalization.[57] Thus, for patients who receive nadolol plus ISMN to prevent variceal rebleeding, the addition of EVL may further reduce rebleeding rate but perhaps at the price of more complications.

Based on these studies, experts specializing in portal hypertension have had different opinions. Garcia-Tsao[58] and Bosch and Garcia-Pahan[59] from Europe suggested that patients with a history of variceal bleeding could receive either β-blocker or EVL to prevent rebleeding, whereas the combination of EVL and nadolol could be reserved for patients in whom EVL or β-blocker alone has failed. On the other hand, Boyer from the United States suggested that β-blockers should be combined with EVL as the treatment of choice to prevent recurrent variceal hemorrhage.[60] β-blockers should be employed during the course of EVL as well as after variceal obliteration for preventing variceal recurrence.

TIPS

TIPS has been developed for more than 20 years to treat portal hypertension. In the past decade, TIPS was widely applied to prevent gastroesophageal variceal rebleeding in the West, but the use of TIPS in Taiwan is very limited.[61] This may be ascribed to technical difficulty in the context of the predominantly post-necrotic cirrhosis in our country. A meta-analysis of 11 controlled studies comparing TIPS with endoscopic therapy showed that TIPS achieved a mean variceal rebleeding rate of 19% compared with 46% achieved by endoscopic therapy. However, the incidence of hepatic encephalopathy was 2-fold in patients treated with

Table 2. Controlled studies of endoscopic variceal ligation (EVL) *vs.* EVL plus nadolol (EVL + N) to prevent variceal rebleeding

Study	Patients (*n*)	Therapy	Rebleeding (%)	Complication (%)	Mortality (%)
Lo et al[54]	62/60	EVL/EVL + N	29/12*	8/11	32/17
de la Pena et al[55]	37/43	EVL/EVL + N	38/14*	3/33*	11/11

**Significant difference.*

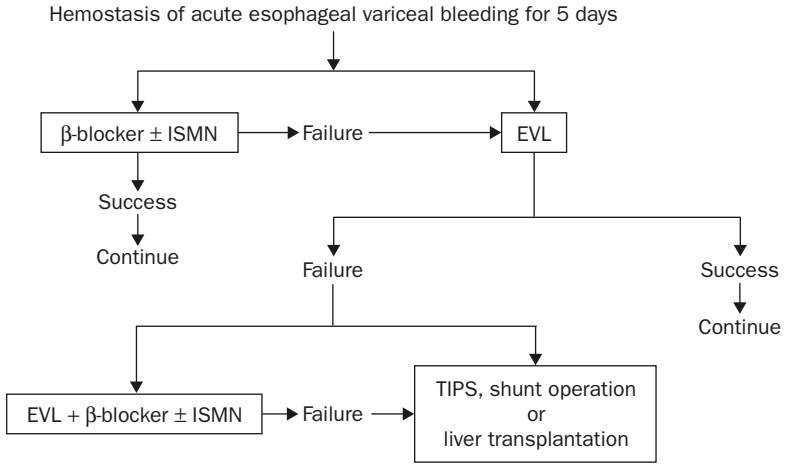

Figure 1. Algorithm for prevention of esophageal variceal rebleeding. ISMN = isosorbide mononitrate; EVL = endoscopic variceal ligation; TIPS = transjugular intrahepatic portosystemic stent shunt.

TIPS compared to patients treated with endoscopic therapy. The survival was similar between the 2 modes of therapy.[62] Moreover, the placement of TIPS requires frequent interventions to maintain TIPS patency. A coated stent has been developed to reduce stent occlusion.[63] Whether or not TIPS using a coated stent could have a lower incidence of hepatic encephalopathy and improved survival awaits further study. Currently, TIPS is reserved as a rescue therapy for pharmacologic or endoscopic therapy failure in the prevention of gastroesophageal variceal rebleeding and as a bridge to liver transplantation.[64]

Summary

There are several methods that a clinician may choose from for the prevention of variceal rebleeding. Either nadolol (alone or combined with ISMN), EVL or a combination of nadolol and EVL (or plus sucralfate) can be employed as first-line treatment. To avoid complications and to avoid the discomfort induced by endoscopic therapy, a combination of nadolol and ISMN can be the first choice. If rebleeding occurs, then EVL can be tried. If patients are tolerant, repeated EVL until variceal obliteration can be performed. If rebleeding continues to occur after taking preventive measures, EVL together with nadolol becomes the treatment of choice. For patients who have contraindications or who are intolerant to β-blockers, EVL is the only choice. A combined approach with EVL and nadolol can be used as first-line treatment or reserved until pharmacologic or endoscopic therapy failure. Shunt operation and TIPS are recommended to be reserved for esophageal varices that are difficult to manage by medical modalities. If patients belong to Child-Pugh class C with repeated variceal bleeding, they should be put on the waiting list for liver transplantation. The algorithm for prevention of esophageal variceal hemorrhage is shown in Figure 1. For patients with variceal rebleeding under control, regular screening for occurrence of hepatocellular carcinoma is advised.[65]

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